Abbreviated Drug Class Review: Proton Pump Inhibitors

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Objectives

1. To provide an abbreviated review of the five proton pump inhibitors (PPIs) currently available by prescription in the U.S. for the treatment of acid-related gastrointestinal disorders (Table 1).[a]
2. To provide a brief comparison of the proprietary and nonproprietary (generic) preparations of omeprazole and of the five PPIs to aid in negotiating contracts for these agents for the Veterans Health Administration.

Table 1 Proton pump inhibitors

PPI	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Proprietary products					
Brand Name	Nexium	Prevacid Prevacid SoluTabs	Prilosec	Protonix	Aciphex
Manufacturer	AstraZeneca	TAP Pharm	Astra	Wyeth-Ayerst	Eisai/Janssen
Nonproprietary products					
Manufacturer	—	—	Kremers Urban / Schwarz	—	—

Formulations

The main difference between proprietary and generic omeprazole formulations result from the manufacturing process. Each capsule of Prilosec® contains enteric-coated granules, the cores of which consist of omeprazole and an alkaline-reacting compound. Each capsule of generic omeprazole contains identical, enteric-coated microtablets, the cores of which contain omeprazole without an alkaline-reacting compound.

The two products also differ in capsule strengths and appearance. Prilosec is available in 10-, 20-, and 40-mg amethyst or apricot / amethyst capsules. Generic omeprazole comes in only two strengths (10 and 20 mg) and the capsules are white or gold / white. The 10-mg capsule of generic omeprazole contains 10 microtablets and the 20-mg capsule contains 18 microtablets.

Proprietary omeprazole but not generic omeprazole has been used off-label as an extemporaneously formulated bicarbonate-based suspension (Simplified Omeprazole Suspension).[1-5] Studies are needed to determine whether generic omeprazole may be substituted for proprietary omeprazole to make Simplified Omeprazole Suspension.

Esomeprazole and lansoprazole are also formulated as capsules containing enteric-coated pellets and granules, respectively. Pantoprazole and rabeprazole are available in tablets. Lansoprazole has two additional FDA-approved oral dosage forms, the orally disintegrating tablets and granules for liquid suspension for individuals with difficulty swallowing capsules (not for enteral tube administration). Like proprietary omeprazole, lansoprazole has been prepared off label as a bicarbonate-based suspension (Simplified Lansoprazole Suspension, SLS).[3, 6-8] Only pantoprazole is available in an intravenous formulation.

The oral PPIs also differ in excipients. Both proprietary and generic omeprazole contain lactose, while the other PPIs do not.

[a] This review does not include nonprescription omeprazole magnesium (Prilosec 1, Procter and Gamble), now available in salmon-colored, 20.6-mg tablets (equivalent to 20 mg omeprazole).

Table 2 Proprietary Proton Pump Inhibitor Formulations

PPI	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Main Oral Dosage Form	DR Caps	DR Caps	DR Caps	DR EC Tabs	DR EC Tabs
Contents of Capsules	EC Pellets	EC Granules	EC Granules	—	—
Strength (Color)	20, 40 mg (Amethyst)	15 mg (Pink / Green) 30 mg (Pink / Black)	10 mg (Apricot / Amethyst) 20 mg (Amethyst) 40 mg (Apricot / Amethyst)	20, 40 mg (Yellow)	20 mg (Lt yellow)
Excipients	Talc	Sucrose	Lactose, Mannitol	Mannitol	Mannitol
Other Dosage Forms	—	*DR Orally Disintegrating Tabs* 15, 30 mg (White / Orange) *DR Susp* (30 ml): 15, 30 mg *Simplified Lansoprazole Suspension*† 30 mg/10 ml (OLU)	*Simplified Omeprazole Suspension*† 20 mg/10 ml (OLU)	*I.v. injection*: 40 mg / vial	—

Caps = Capsules; DR = Delayed-release; EC = Enteric-coated; I.v. = Intravenous; OLU = Off-label Use; Susp = Suspension; Tabs = Tablets

† Bicarbonate-based simplified suspensions of lansoprazole and omeprazole are extemporaneously compounded. Simplified Lansoprazole Suspension: 3 mg/ml 8.4% sodium bicarbonate; stable for 14 days at room temperature or 28 days refrigerated (non-oral syringe).[7] Simplified Omeprazole Suspension: 2 mg/ml 8.4% sodium bicarbonate; stable for 1 week at room temperature or 24 weeks frozen (non-oral syringe); protect from light.[1]

Table 3 Nonproprietary proton pump inhibitor formulation

PPI	Omeprazole
Brand Name	—
Manufacturer	Kremers Urban / Schwarz
Main Oral Dosage Form	DR Caps
Contents of Capsules	EC Microtablets
Strength (Color)	10 mg (White) 20 mg (Gold / White)
Excipients	Lactose
Other Dosage Forms	—

Caps = Capsules; DR = Delayed-release

Indications and Dosage

The PPIs are FDA-approved for a variety of gastrointestinal acid-related disorders (see Table 4). The approved therapeutic indications, dosage and administration recommendations, as well as the clinical studies described in the package inserts for nonproprietary omeprazole and proprietary omeprazole (Prilosec) are identical.[9, 10]

Lansoprazole and omeprazole have the greatest number of approved indications for management of duodenal ulcers, gastric ulcers, GERD, or pathologic hypersecretory conditions.

Table 4 FDA-approved indications, off-label uses (OLUs), and dosages for PPIs

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Duodenal ulcers					
Healing	—	15 mg q.d. × 4 wk	20 mg q.d. × 4 to 8 wk	40 mg q.d. × 2 to 4 wk (OLU)	20 mg q.d. × ≥ 4 wk
Maintain healing	—	15 mg q.d.	10 to 20 mg q.d. (OLU)	—	—
Eradicate *Helicobacter pylori* associated with duodenal ulcers	40 mg q.d. × 10 d in 3-drug regimen†	30 mg b.i.d. × 10 or 14 d in 3-drug regimen† 30 mg q8h x 14 d in 2-drug regimen†	20 mg b.i.d. x 10 d in 3-drug regimen† 40 mg q.d. × 14 d in 2-drug regimen†	—	20 mg b.i.d. × 7 d in 3-drug regimen†
Prevention of re-bleeding of high-risk duodenal ulcers	—	—	20 mg q6h or 40 mg q12h x 5 d (OLU)	—	—
Gastric ulcers					
Healing, non-NSAID–related	—	30 mg q.d. × ≤ 8 wk	40 mg q.d. × 4 to 8 wk	40 mg q.d. × 4 or 8 wk (OLU)	20 mg q.d. × 3 or 6 wk (OLU)
Healing, NSAID-related	—	30 mg q.d. × 8 wk	—	40 mg q.d. × 12 wk (OLU)	—
Reduce risk, NSAID-related	—	15 mg q.d. × ≤ 12 wk	—	40 mg q.d. × 12 wk (OLU)	—
Prevention of re-bleeding after acute bleeding of high-risk, gastric ulcers	—	—	20 mg q6h or 40 mg q12h x 5 d (OLU)	—	—
GERD					
Relieve symptoms	20 mg q.d. × 4 wk	15 mg q.d. × ≤ 8 wk	(NERD) 20 mg q.d. × 4 wk	40 mg q.d. × 4 or 8 wk (OLU)	20 mg q.d. × 4 to 8 wk
Maintain symptom control in nonerosive reflux disease, on-demand therapy	20 mg q.d. p.r.n. (OLU)	—	20 mg q.d. p.r.n. (OLU)	—	—
Healing of erosive or ulcerative esophagitis	20 or 40 mg q.d. × 4 to 8 wk	30 mg q.d. × 8 to 16 wk	20 mg q.d. × 4 to 8 wk	40 mg q.d. × 8 to 16 wk	20 mg q.d. × 4 to 8 wk
Maintain healing of erosive or ulcerative esophagitis	20 mg q.d.	15 mg q.d.	20 mg q.d.	40 mg q.d.	20 mg q.d.
Maintain healing of erosive or ulcerative esophagitis, alternate-day dosing	—	30 mg q.o.d. (OLU)	20 to 40 mg q.o.d. (OLU-N)	—	—
Short-term treatment of GERD with history of erosive esophagitis, as an alternative to oral therapy	—	—	—	40 mg q.d. × 7 to 10 d (i.v.)	—
Posterior laryngitis, GERD-related	—	—	20 or 40 mg q.h.s. × 6 to 24 wk or 20 to 40 mg b.i.d. × 4 to 12 wk (OLU)	—	—
Diagnosis of GERD-related noncardiac chest pain	—	30 mg q.d. x 4 wk (OLU)	20 mg b.i.d. x 14 d (OLU)	—	—
Hypersecretory conditions	—	60 to 180 mg/d in 1 or 2 divided doses	60 to 360 mg/d in 1 to 3 divided doses	80 mg/d (p.o.) or 160 mg/d (i.v.) in 2 divided doses, up to 240 mg/d	60 or 120 mg/d in 1 or 2 divided doses

Sources: [9-53]

All doses refer to oral administration except as indicated.

OLU = Off-label use supported by at least one published double-blind, randomized controlled trial comparing PPI to placebo or active comparator or rated as having at least "fair" documentation in *Off-Label Drug Facts* (2003).[25] Abstracts are excluded.

OLU-N = Off-label use supported by at least one noncomparative, double-blind, randomized trial or at least one comparative open-label randomized trial. Abstracts are excluded.

NERD = Non-erosive (endoscopy-negative) reflux disease

† Esomeprazole, omeprazole, lansoprazole, and rabeprazole are approved for *H. pylori* eradication in three-drug combinations with amoxicillin (1 gm) and clarithromycin (500 mg) given twice daily. Lansoprazole (with amoxicillin 1 gm) and omeprazole (with clarithromycin 500 mg) are also approved for the same indication in two-drug combinations.

Lansoprazole is the only PPI approved for healing or risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-related gastric ulcers, and there is off-label experience with pantoprazole for this indication.[11] Off-label use of pantoprazole in the management of duodenal and gastric ulcers has been documented in a number of double-blind randomized controlled trials (DBRCTs).[12-19]

All of the PPIs have approved indications for treatment of erosive or ulcerative reflux esophagitis. Healing and maintenance of erosive esophagitis are currently the main approved indications for pantoprazole, which is the first PPI available in a parenteral (intravenous) formulation for the short-term (7- to 10-day) treatment of GERD in patients who are unable to continue taking the oral tablets. Omeprazole has dosing recommendations specifically for treatment of non-erosive reflux disease.

All of the PPIs except esomeprazole have approved indications for the treatment of pathologic hypersecretory conditions such as Zollinger-Ellison syndrome.

There is sufficient evidence to support unique off-label uses for omeprazole, lansoprazole, and esomeprazole. Orally administered omeprazole has been used for prevention of re-bleeding of peptic ulcers with high-risk endoscopic stigmata following endoscopic therapy[49, 50] and for treatment of reflux laryngitis.[25, 46] Alternate-day dosing of either lansoprazole or omeprazole has been reported to be effective in preventing recurrence of erosive esophagitis.[25] Esomeprazole[52] and omeprazole[53] given on-demand for up to 6 months have been shown to be efficacious in controlling heartburn in patients with nonerosive (endosocopy-negative) reflux disease, with esomeprazole 40 mg no better than 20 mg daily as needed[54] and omeprazole 20 mg superior to 10 mg daily as needed.[53] Standard-dose lansoprazole (30 mg per day)[48] and double-dose omeprazole (40 mg per day)[47] have also been useful in the diagnosis of noncardiac chest pain associated with GERD.

Dosing in special patient populations

Dosage adjustment of the PPIs may be necessary in patients with hepatic impairment (Table 5). None of the PPIs require dosage adjustment in renal impaired or elderly patients. Race-related pharmacokinetic differences have been noted in Asian patients treated with lansoprazole, omeprazole, and rabeprazole.

Table 5 Dosage adjustments in special populations

Population characteristic	Esomeprazole magnesium	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Hepatic impairment	Severe impairment (Child Pugh Class C): Max. ≤ 20 mg q.d.	Severe impairment: decrease dose	Consider decrease in dose	No adjustment (highest dose used, 40 mg q.d.)	Severe impairment: use caution
Renal impairment	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Elderly	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Gender	No adjustment	No adjustment	No data	No adjustment	No adjustment
Race	No data	Limited data suggests increased AUC in Asians; no dosing recommendations	Consider decreasing dose in Asians	No data	AUC increased 50% to 60% in Japanese using different formulations; no dosing recommendations

Sources: [9, 10, 21-24]

Compliance factors

Alternative dosing packages or methods of administration that may improve patient convenience or aid patient adherence to medication regimens are available for all of the PPIs except rabeprazole (Table 6). According to the manufacturer (Janssen Pharmaceutica, Inc., product information, verbal communication, October 2003), there are currently no alternative methods of administration for rabeprazole (which is available only as delayed-release tablets that must be swallowed whole) in patients who have difficulty swallowing or are unable to take oral medication.

Generic omeprazole capsules may be opened and the microtablets sprinkled on applesauce. Unlike proprietary omeprazole, the stability and pH effects of generic omeprazole mixed in orange juice have not been studied.

Table 6 Alternative methods of administration

Indication / Problem	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole
H. pylori eradication	—	*Prevpac*® (lansoprazole / amoxicillin / clarithromycin) dosing package	—	—
Difficulty swallowing capsules	Open capsule and sprinkle pellets in applesauce, tap water, orange juice, apple juice, or yogurt.	*Delayed-release capsules*. Open capsule and sprinkle granules in applesauce, *Ensure* pudding, cottage cheese, yogurt, or strained pears. Alternatively, mix granules in 60 ml of apple, orange, or tomato juice and swallow immediately. *Orally disintegrating tablets*. Place tablet on tongue, allow to disintegrate (about 1 minute), then swallow. *Delayed-release oral suspension*. Note: not recommended for administration via enteral tubes.	Open capsule and sprinkle granules (proprietary product) or microtablets (nonproprietary product) in applesauce. Orange juice has also been used with proprietary omeprazole (OLU).[55]	—
Enteral tube administration	—	Open capsules, mix intact granules with about 40 ml of apple juice (not other liquids) , then inject into NG tube. Extemporaneously compounded Simplified Lansoprazole Suspension (OLU).†	Open capsules of proprietary omeprazole, mix intact granules with orange juice, then inject into enteral tube (OLU).[3] Extemporaneously compounded Simplified Omeprazole Suspension (OLU). †	—
Unable to continue oral medication	—	—	—	Intravenous formulation

NG = Nasogastric; OLU = Off-label use

† Bicarbonate-based simplified suspensions of lansoprazole and omeprazole are extemporaneously compounded. Simplified Lansoprazole Suspension: 3 mg/ml 8.4% sodium bicarbonate; stable for 14 days at room temperature or 28 days refrigerated (non-oral syringe).[7] Simplified Omeprazole Suspension: 2 mg/ml 8.4% sodium bicarbonate; stable for 1 week at room temperature or 24 weeks frozen (non-oral syringe); protect from light.[1]

Safety

Common adverse events

All of the available PPIs have been well tolerated in short- and long-term clinical trials.[9, 10, 21-24, 45] The estimated number of patients exposed to the PPIs during the premarketing clinical trials are 10,000 for esomeprazole, more than 10,000 for lansoprazole, 3096 for omeprazole, more than 11,000 for pantoprazole, and 2900 for rabeprazole. The adverse event information for generic omeprazole is identical to that for proprietary omeprazole.

The most frequently reported adverse events (those occurring in greater than or equal to 2% of patients in at least one treatment group for any PPI) in placebo-controlled trials generally affected the gastrointestinal or central nervous system (Table 7). Headache, diarrhea, and abdominal pain were usually the most common adverse events. The frequency of headache with lansoprazole occurred in more than 1% of patients (N > 10,000) but was more common on placebo. Dose-related increases in the frequency of diarrhea were noted in premarketing clinical trials for lansoprazole. For the other PPIs, dose-related adverse events were either not observed (pantoprazole, rabeprazole) or not reported (esomeprazole, omeprazole). Overall, the adverse event profiles of the PPIs in placebo-controlled trials were similar.

Pooled results of premarketing head-to-head trials[21, 24] and other direct comparisons of PPIs (omeprazole versus other PPIs, and lansoprazole versus esomeprazole or pantoprazole) in DBRCTs have consistently found the safety and tolerability of PPIs to be similar.[12, 17, 18, 24, 29, 31-33, 56-81] One exception was a crossover DBRCT that found rabeprazole to be superior to omeprazole for "absence of unwanted side effects" and "presence of positive side effects" ($p = 0.0467$ and $p = 0.0188$, respectively).[82] There was, however, no significant treatment difference in total treatment preference score (the primary efficacy variable) and no difference in tolerability.

Table 7 Most frequently occurring adverse events in placebo-controlled trials (≥ 2% of patients in at least one treatment group for any PPI)

	Frequency as percentage (%) of patients [Rates in brackets refer to adverse events considered by the investigator to have possible, probable, or definite relationship to drug.]				
Adverse Event	**Esomeprazole**	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
N (Exposed)	**NR**	**2768**	**465**	**521**	**1552**
Central Nervous System					
Headache	[3.8]	[> 1%]	2.9 [2.4]* to 6.9*	[6]	[2.4]*
Gastrointestinal System					
Abdominal pain	[3.8]	[2.1]*	2.4 [0.4] to 5.2	[1]	NR
Diarrhea	[4.3]	[3.8]*	3.0 [1.9] to 3.7*	[4]*	NR
Flatulence	—	< 1	2.7	[2]	NR
Nausea	—	[1.3]*	2.2 [0.9] to 4.0	[2]	NR
Vomiting	—	< 1	1.5 [0.4]	[2]	NR

Sources: Package inserts[9, 10, 21-24]

Rates are not directly comparative between PPIs because the frequencies reflect the results of different clinical trials, the method of collecting adverse event data in the trials may have differed, and the presentation of adverse events in package inserts varied.

NR = Not reported. NR for adverse event rate means that the adverse event was listed and was not rare (not ≤ 1/1000), but the frequency was not specified. Dash marks indicate adverse event was not mentioned in the package insert under placebo-controlled trials; however, the adverse event may have been reported in other comparative clinical trials.

* Frequency of adverse event was greater on PPI than on placebo (no statistical analyses).

Studies in rats have found PPI-induced hyperplasia of gastric enterochromaffin-like (ECL) cells and, in some cases, gastric neuroendocrine cell tumors, which may result from chronic hypergastrinemia.[9, 10, 21-24, 45] Time- and dose-related increases in the frequency of ECL cell hyperplasia and hypergastrinemia have been observed in patients treated with PPIs for 6 months to 5 years in clinical trials.[9, 10, 21-24, 45, 83] No dysplastic or neoplastic changes of the ECL cells in the gastric mucosa have been detected and no patient has developed the carcinoid tumors observed in rats.

Postmarketing Adverse Events

Voluntarily reported adverse events associated with postmarketing experience with the PPIs have been disclosed in the package inserts for all the PPIs.[9, 10, 21-24] Postmarketing adverse events have generally been consistent with short-term use of the PPIs and no clear differences between agents have been noted. Blood dyscrasias and serious allergic reactions have been reported. In many cases, a relationship with the PPI could not be established.

Drug Interactions

Drug-Drug Interactions

The two main mechanisms of drug-drug interactions relevant to PPIs are (1) inhibition or induction of CYP450 isoenzymes, and (2) alteration of drug absorption. These interactions are summarized in Table 8.

Omeprazole seems to have the greatest potential to cause CYP450-mediated drug interactions, while lansoprazole, pantoprazole and rabeprazole are less likely to result in such interactions.[84-86] Omeprazole inhibits CYPs 2C9 and 2C19. In extensive metabolizers, the inhibition of these isoenzymes by omeprazole has resulted in significant decreases in the clearances of phenytoin, diazepam, and possibly carbamazepine and S-warfarin.[87] Esomeprazole may reduce the clearance of diazepam by 45% (similar to omeprazole), cause small reductions in phenytoin and R-warfarin metabolism, and cause a small alteration in a minor CYP2C19 metabolic pathway of cisapride.[88] Rabeprazole is about half as potent as omeprazole in inhibiting CYP2C19 and does not interact with diazepam. CYPs 1A1, 1A2, and 3A4 are induced by omeprazole and lansoprazole but these interactions do not appear to be of clinical relevance, with the exception of a possible reduction in efficacy of oral contraceptives by lansoprazole.[86, 87]

PPIs may decrease or increase the bioavailability of other drugs whose absorption is dependent on gastric pH (see Table 8). The profound inhibition of gastric acid secretion by PPIs results in decreased plasma concentrations of ampicillin, iron salts, and ketoconazole. The same mechanism was the proposed explanation for decreased plasma concentrations of indinavir when given concomitantly with omeprazole.[89] PPIs are also expected to reduce the absorption of atazanavir[90] and delavirdine.[91] Increases in digoxin bioavailability have occurred with omeprazole (10% increase in area under the curve)[92] and rabeprazole (19% increase).[23, 93]

There are few clinically relevant drug interactions with the PPIs.[86] The most important interaction appears to be the 25% to 50% reduction in clearance of diazepam by omeprazole or esomeprazole via CYP2C19 inhibition in extensive metabolizers,[86, 88] although a similar degree of change in diazepam clearance due to cimetidine was found to be of little clinical consequence.[94] Other CYP450-metabolized benzodiazepines also have potential to be affected (see Table 8). Possibly clinically relevant interactions due to altered drug absorption are decreases in concentrations of azole antifungal agents (itraconazole, ketoconazole) and antiretroviral agents (atazanavir, delavirdine, indinavir) and increases in digoxin concentrations.

Interactions between warfarin or phenytoin and the PPIs, including omeprazole, do not seem to be clinically relevant when studied in controlled trials.[86] However, according to FDA adverse event and drug interaction data since drug launch, the most common type of reported interaction with omeprazole, lansoprazole, or pantoprazole involved vitamin K antagonists (e.g., warfarin).[95] Although pantoprazole is considered to be free of clinically relevant drug interactions, interactions with vitamin K antagonists were reported at similar rates for all three PPIs, albeit rarely. Reports of interactions between these three PPIs and benzodiazepines or phenytoin were even rarer. The FDA postmarketing adverse event data suggest that there is a class effect for interactions between vitamin K antagonists and PPIs, and these interactions may be clinically relevant in certain individuals.

Differences in CYP2C19 genotype have been reported to influence *H. pylori* infection cure rates in dual-drug[96] and triple-drug[97, 98] regimens with omeprazole and lansoprazole, although other studies have found no effect.[99-101] Clarithromycin has also been shown to increase omeprazole concentrations irrespective of CYP2C19 genotype status,[102] and this interaction could theoretically improve *H. pylori* infection cure rates. Cure rates with rabeprazole, which should be less affected by CYP2C19 genotype, have been conflicting. It has been found to be similar[98, 101] or inferior[103] to lansoprazole, and similar to omeprazole [100, 103] in triple-drug regimens in extensive metabolizers. Resistance to clarithromycin seems to have a bigger impact on cure rates than CYP2C19 genotype.[98, 99, 101]

In summary, few clinically relevant drug-drug interactions are expected with the PPIs. The main clinically relevant difference between PPIs in terms of drug interactions seems to be the potential for omeprazole- or esomeprazole-induced increases in the effects of diazepam and possibly other CYP450-metabolized benzodiazepines. Reduction of the benzodiazepine dose, use of a benzodiazepine that is metabolized by glucuronidation (lorazepam, oxazepam, or temazepam), or the use of another PPI may be a consideration in individuals who develop an adverse interaction from the drug combination.

Table 8 Selected drug interactions involving the proton pump inhibitors

		Object drugs that may interact with the proton pump inhibitors				
Mechanism	**Effect of object drug**	**Esomeprazole**	**Lansoprazole**	**Omeprazole**	**Pantoprazole**	**Rabeprazole**
CYP450 inhibition	↑	Benzodiazepines Alprazolam Chlordiazepoxide Clonazepam Diazepam[†] Flurazepam Midazolam Triazolam Cisapride Phenytoin Warfarin[†]	Warfarin[†]	Benzodiazepines Alprazolam Chlordiazepoxide Clonazepam Diazepam[†] Flurazepam Midazolam Triazolam Carbamazepine[†] Clarithromycin[↔] Cyclosporin[†] Disulfiram Phenytoin[†] Warfarin[†]	Warfarin[†]	Clarithromycin[↔] Cyclosporin[†] Warfarin[†]
CYP450 induction	↓	—	OCPs (?)[†] Theophylline	Caffeine	—	—
Decrease GI absorption	↓	Ampicillin Atazanavir[†] Delavirdine[†] Indinavir[†] Iron salts Itraconazole[†] Ketoconazole[†]	Ampicillin Atazanavir[†] Delavirdine[†] Indinavir[†] Iron salts Itraconazole[†] Ketoconazole[†]	Ampicillin Atazanavir[†] Delavirdine[†] Indinavir[†] Iron salts Itraconazole[†] Ketoconazole[†]	Ampicillin Atazanavir[†] Delavirdine[†] Indinavir[†] Iron salts Itraconazole[†] Ketoconazole[†]	Ampicillin Atazanavir[†] Delavirdine[†] Indinavir[†] Iron salts Itraconazole[†] Ketoconazole[†]
Increase GI absorption	↑	Digoxin[†]	Digoxin[†]	Digoxin[†]	—	Digoxin[†]

Sources: [9, 10, 21-24, 84-93, 95, 102, 104-106]

The list of drugs in this table is not intended to be all-inclusive. Consult appropriate references for a comprehensive list of drugs that may interact with proton pump inhibitors.

OCP = Oral contraceptive pills

† Potential clinically relevant interaction. Increased INR and prothrombin time in patients taking warfarin / vitamin K antagonists and omeprazole, lansoprazole, or pantoprazole have been the most frequently reported drug interaction involving PPIs reported to the FDA, although the frequency was rare.[95] All PPI package inserts report a potential interaction with warfarin.[9, 10, 21-24]

↔ Two-way interaction; clarithromycin may increase plasma omeprazole and esomeprazole concentrations. Omeprazole may increase plasma clarithromycin and 14-hydroxyclarithromycin concentrations. Esomeprazole may increase plasma 14-hydroxyclarithromycin concentrations.

? Unclear effect

Drug-Lab Interactions

Pantoprazole has been associated with false-positive results for tetrahydrocannabinol (THC) on urine screening tests.[21]

Clinical Efficacy

Comparative PPI doses were based on the results of 40 DBRCTs or systematic reviews that compared the PPIs primarily with omeprazole (see Table 9). The relative efficacies were based on subjective (symptom relief) or objective (e.g., endoscopic or pH-metric) measures of response to treatment in patients with duodenal ulcers, *Helicobacter pylori* infection, gastric ulcers, gastroesophageal reflux disease, erosive esophagitis, or dyspepsia.

Table 9 Comparative doses of PPIs

Relative efficacy of PPIs (Doses in mg)		
OME 10	**OME 20**	**OME 40 or 20 b.i.d.**
= LAN 15	≤ ESO 20 or 40 ≥ LAN 15 ≤ LAN 30 = PAN 40 ≤ RAB 20	= ESO 20 b.i.d. = LAN 30 > LAN 30 b.i.d.† > PAN 40 b.i.d.† = RAB 20
LAN 15	**LAN 30**	**LAN 30 b.i.d.**
< ESO 20	= PAN 40 < ESO 40	= PAN 40 b.i.d.

Sources: [12, 17, 18, 24, 29, 31-33, 56-81, 107, 108]

The comparative doses of proton pump inhibitors (PPIs) were based on relative efficacies reported in double-blind, randomized controlled trials or systematic reviews in patients with gastrointestinal acid-related disorders. Most of the evaluated trials compared lansoprazole or other proton pump inhibitors (PPIs) with omeprazole. Relative efficacy was based on subjective or objective measures of response to treatment in patients with duodenal ulcers, *Helicobacter pylori* infection, gastric ulcers, gastroesophageal reflux disease, erosive esophagitis, or dyspepsia. No trials comparing PPIs in pathologic hypersecretory conditions were found by the literature search.

ESO = Esomeprazole; LAN = Lansoprazole; OME = Omeprazole; PAN = Pantoprazole; RAB = Rabeprazole

= Comparable to; ≤ Inferior or comparable to; ≥ Superior or comparable to

† Unexpected result; see text

In general, standard doses of PPIs (esomeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg) seem to be therapeutically comparable. However, standard-dose omeprazole may be inferior to standard doses of lansoprazole or rabeprazole. Double-dose omeprazole seems to have improved efficacy, as it has been found to be similar in efficacy to standard-dose lansoprazole or rabeprazole. Likewise, half-doses of PPIs are comparable to each other and inferior to standard doses.

Double doses of a PPI are generally comparable to or better than standard doses and comparable to double doses of other PPIs. The results of a small DBRCT (N = 30) were unexpected in this regard. The study compared twice daily doses of lansoprazole 30 mg, omeprazole 20 mg, and pantoprazole 40 mg as maintenance therapy in patients with severe reflux esophagitis complicated by stricture.[76] After 4 weeks of treatment, omeprazole (9 of 10, 90%) was statistically significantly superior to either lansoprazole (2 of 10, 20%) or pantoprazole (3 of 10, 30%) in maintaining remission, defined as absence of esophagitis and stricture on endoscopy and absence of symptoms ($p < 0.01$ for each analysis). No statistically significant difference was noted between lansoprazole and pantoprazole. The authors attributed the treatment differences to intra- and interindividual variability in lansoprazole absorption and to pH-dependent differences in reactivity between omeprazole and pantoprazole in inhibiting H+/K+-ATPase. Further clinical trials in large patient populations are needed to evaluate relative antisecretory efficacies of PPIs given twice daily.

Therapeutic Interchangeability

Three unpublished studies demonstrated that generic omeprazole is bioequivalent to proprietary omeprazole in healthy volunteers in the fasting state, after food intake, and when the contents of the capsules are sprinkled on applesauce (L. Hinman, Regulatory Affairs, Schwarz Pharma, verbal communication, October 2003). Generic omeprazole is AB-rated by the FDA and is considered to be therapeutically equivalent to proprietary omeprazole.

Six published studies evaluated therapeutic interchange of PPIs: four retrospective analyses from the VA (including a case-control study),[109-112] one prospective survey from a managed care organization,[113] and one crossover DBRCT from the U.K.[82] The U.K. study involved switching between omeprazole and rabeprazole, and the remaining five studies involved conversion from omeprazole to lansoprazole.

In two VA studies that reported conversion rates (Table 10), successful conversion was possible in 72% and 95% of patients switched from omeprazole to lansoprazole.[109, 112] Of patients who could not be adequately maintained on lansoprazole in three VA studies, 54% to 72% had unsuccessful conversion because of lack of efficacy and 28% to 45%, because of adverse effects.[109, 110, 112] The most common adverse effects were diarrhea and abdominal or chest pain.[110, 112] One study reported that 94% of patients who were unsuccessfully converted to lansoprazole improved after switching back to omeprazole, and only 8% would consider trying lansoprazole again.[112]

Table 10 Published Therapeutic Interchange Studies in the VA: Converting from Omeprazole to Lansoprazole

Reference	Median Dose (Range), mg/d	Successful Conversion	Unsuccessful Conversion	Reason for Unsuccessful Conversions	
				Lack of Efficacy	Adverse Effects
Amidon (2000)[109]	OME 20 (20 to 60) LAN 30 (15 to 90)	72% (56/78)	28% (22/78)	54.5% (12/22)	45.4% (10/22)
Gerson (2000)[112]	OME 20 (20 p.r.n. to 80)† LAN 30 (15 to ≥ 120)†	95% (3508/3703)	5% (195/3703)	69% (118/172)	30.2% (52/172)
Raisch (2001)[110]	—	—	—	72.5% (37/51)	27.5% (14/51)

† Doses used by 172 lansoprazole-intolerant patients

Subsets of patients may experience uncontrolled symptoms, more adverse effects, or a negative impact on health outcomes when switched from one PPI to another.[82, 109-112] This observation is expected after drug conversion, since individual variability in responses to drugs is seen even within the same therapeutic class. Interestingly, perhaps because of a "placebo effect" following conversion, 39 (33.9%) of 115 patients previously considered stable on omeprazole who were then 'switched' to blinded omeprazole reported adverse effects, and 7 (6.1%) discontinued medication because of them.[82]

Population risk factors for unsuccessful conversion or nonresponse to PPI therapy have been identified in two studies. One study found that patients who worsened after being converted from omeprazole to lansoprazole were significantly younger than patients with stable outcomes (mean age, 49.7 years vs. 57.3 years).[113] A large nested case-control study (N = 558) found that age over 60 years, heavy smoking, and previous use of PPIs were significantly more common in non-responders to lansoprazole compared with responders.[114] Unfortunately, the individuals who will experience unsatisfactory responses cannot be predicted.

Several studies have shown that some individuals who switch PPIs may have a preference for one agent over another.[82, 109, 111] However, factors other than PPI effectiveness may influence patient satisfaction with switching agents, such as the method of administering the therapeutic interchange program.[113]

Overall, the results of these studies support the well-accepted premise that PPIs may be considered therapeutic alternates, and that the majority of patients can be switched from one PPI to another at therapeutically comparable doses (see Table 4 and Table 9) without reduction in effectiveness or tolerability. However, some individuals may be able to distinguish between drugs within the same class and express a preference for one drug over another.

Conclusion

For oral administration, nonproprietary omeprazole can be used for generic substitution of proprietary omeprazole (Prilosec). Proprietary omeprazole should be used for compounding Simplified Omeprazole Suspension and mixing in orange juice until the stability and equivalent intragastric pH effects of generic omeprazole in such formulations can be verified.

The PPIs may be considered for therapeutic interchange because of their comparable pharmacologic properties and clinical efficacy and safety profiles. In general, PPIs are therapeutically comparable at the same dosage levels (half-, standard-, or double-dose). Consistent results of clinical trials in patients with duodenal ulcers, gastric ulcers, GERD, hypersecretory conditions, and other acid-related disorders strongly suggest that there is a class effect of PPIs for these disorders, although differences in dosage formulations and drug interactions may occasionally influence choice of PPI in individual cases.

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